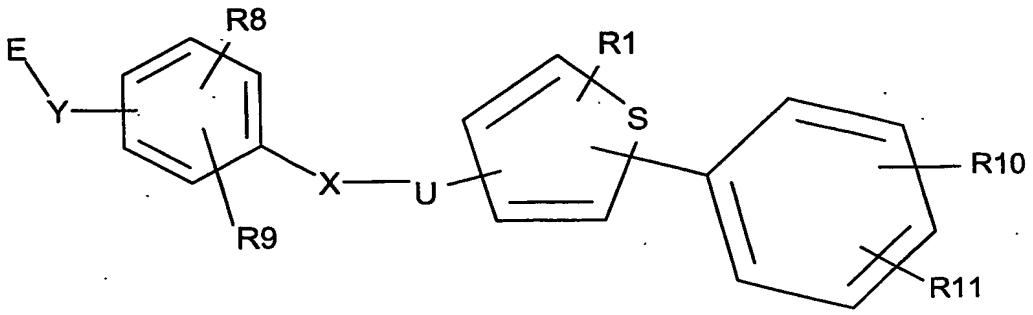
CLAIMS

What is claimed is:

1. A compound of the Formula I':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, phenyl, aryl-C_{1-4}-heteroalkyl, heteroaryl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_8 alkyl is optionally substituted with from one to three substituents independently selected from R1'; and further wherein C_1-C_8 alkenyl, phenyl, aryl-C_{1-4}-heteroalkyl, heteroaryl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, are each optionally substituted with from one to three substituents independently selected from R2;

(b) R1' are each independently selected from the group consisting of hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{1-4}-alkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22,

S(O)R23, $S(O)_2$R24, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2, R26, R27, R28, and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2$R16, $N(R17)_2$, NR18C(O)R19, $NR20SO_2$R21, SR22, S(O)R23, $S(O)_2$R24, and $S(O)_2N(R25)_2$;

(d) X is selected from the group consisting of O, S, $S(O)_2$, N and a bond;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;

(f) Y is selected from the group consisting of C, NH, and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26;

with the proviso that when R1 is C_1-C_8 alkyl, Y is in a para substituted position with relation to X, and X is selected from the group consisting of a bond and O, then R4 is selected from the group consisting of C_1-C_5 alkoxy, aryloxy, and arylC_0-C_4 alkyl; with the additional proviso that when R1 is C_1-C_8 alkyl, Y is in a para substituted position with relation to X, X is S, and U is optionally substituted methylene, then R4 is selected from the group consisting of C_1-C_5 alkoxy, aryloxy, and arylC_0-C_4 alkyl;

(h) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(i) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each

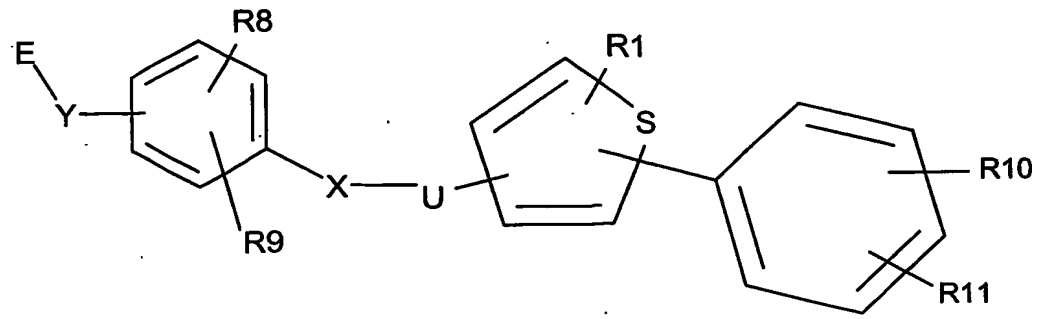
optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

(k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl; and

(l) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31.

2. A compound of the Formula I'':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, phenyl, aryl-C_{1-4}-heteroalkyl, heteroaryl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_8 alkyl is optionally substituted with from one to three substituents independently selected from R1'; and further wherein C_1-C_8 alkenyl, phenyl, aryl-C_{1-4}-heteroalkyl, heteroaryl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, are each optionally substituted with from one to three substituents independently selected from R2;

(b) R1' are each independently selected from the group consisting of hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{1-4}-alkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the

group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2, R26, R27, R28, and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$;

(d) X is selected from the group consisting of O, S, $S(O)_2$, N and a bond;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26;

with the proviso that when R1 is C_1-C_8 alkyl, Y is in a para substituted position with relation to X, and X is selected from the group consisting of a bond and O, then R4 is selected from the group consisting of C_1-C_5 alkoxy, aryloxy, and arylC_0-C_4 alkyl; with the additional proviso that when R1 is C_1-C_8 alkyl, Y is in a para substituted position with relation to X, X is S, and U is optionally substituted methylene, then R4 is selected from the group consisting of C_1-C_5 alkoxy, aryloxy, and arylC_0-C_4 alkyl;

(h) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(i) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected

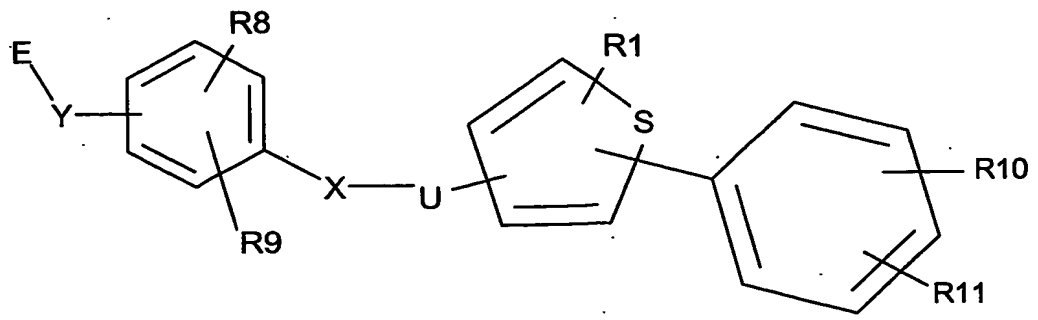
from the group consisting of hydrogen and C_1-C_4 alkyl;

(j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)$_2$R16', N(R17')$_2$, NR18'C(O)R19', NR20'SO$_2$R21', SR22', S(O)R23', S(O)$_2$R24', and S(O)$_2$N(R25')$_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

(k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl; and

(l) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31.

3. A compound of the Formula I''':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(m) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, phenyl, aryl-C_{1-4}-heteroalkyl, heteroaryl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_8 alkyl is optionally substituted with from one to three substituents independently selected from R1'; and further wherein C_1-C_8 alkenyl, phenyl, aryl-C_{1-4}-heteroalkyl, heteroaryl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, are each optionally substituted with from one to three substituents independently selected from R2;

(n) R1' are each independently selected from the group consisting of hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{1-4}-alkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the

group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(o) R2, R26, R27, R28, and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$;

(p) X is selected from the group consisting of O, S, $S(O)_2$, N and a bond;

(q) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;

(r) Y is selected from the group consisting of C, O, S, NH and a single bond;

(s) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26;

with the proviso that when R1 is C_1-C_8 alkyl, Y is in a para substituted position with relation to X, and X is selected from the group consisting of a bond and O, then R4 is selected from the group consisting of C_1-C_5 alkoxy, aryloxy, and arylC_0-C_4 alkyl; with the additional proviso that when R1 is C_1-C_8 alkyl, Y is in a para substituted position with relation to X, X is S, and U is optionally substituted methylene, then R4 is selected from the group consisting of C_1-C_5 alkoxy, aryloxy, and arylC_0-C_4 alkyl;

with the further proviso that when Y is O then R4 is selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26;

(t) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(u) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

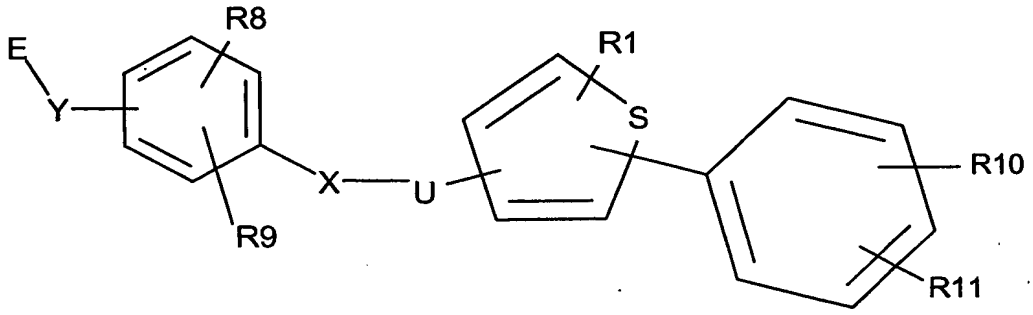
(v) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

(w) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl; and

(x) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-

C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31.

4. A compound of the Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, phenyl, aryl-C_{1-4}-heteroalkyl, heteroaryl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_8 alkyl is optionally substituted with from one to three substituents independently selected from R1'; and further wherein C_1-C_8 alkenyl, phenyl, aryl-C_{1-4}-heteroalkyl, heteroaryl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, are each optionally substituted with from one to three substituents independently selected from R2;

(b) R1' are each independently selected from the group consisting of hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl,

C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{1-4}-alkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2, R26, R27, R28, and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$;

(d) X is selected from the group consisting of O, S, $S(O)_2$, N, and a bond;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker may be replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with

from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26;

with the proviso that when R1 is C_1-C_8 alkyl, Y is in a para substituted position with relation to X, and X is selected from the group consisting of a bond and O, then R4 is selected from the group consisting of C_1-C_5 alkoxy, aryloxy, and arylC_0-C_4 alkyl; with the additional proviso that when R1 is C_1-C_8 alkyl, Y is in a para substituted position with relation to X, X is S, and U is optionally substituted methylene, then R4 is selected from the group consisting of C_1-C_5 alkoxy, aryloxy, and arylC_0-C_4 alkyl;

(h) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(i) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-

C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

(k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl; and

(l) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are

each optionally substituted with from one to three substituents each independently selected from R31.

5. A compound as claimed by any one of Claims 1 through 4 wherein X is -O-.

6. A compound as claimed by any one of Claims 1 through 4 wherein X is -S-.

7. A compound as claimed by any one of Claims 1 through 6 wherein R4 is selected from the group consisting of C_1-C_5 alkoxy, aryloxy, and arylC_0-C_4 alkyl.

8. A compound as claimed by any one of Claims 2 through 7 wherein Y is O.

9. A compound as claimed by any one of Claims 1 through 7 wherein Y is C.

10. A compound as claimed by any one of Claims 1 through 7 wherein Y is S.

11. A compound as claimed by any one of Claims 1 through 10 wherein E is C(R3)(R4)A.

12. A compound as claimed by any one of Claims 1 through 11 wherein A is carboxyl.

13. A compound as claimed by any one of Claims 1 through 12 wherein R1 is H.

14. A compound as claimed by any one of Claims 1 through 12 wherein A is COOH and R1 is H.

15. A compound as claimed by any one of Claims 1 through 14 wherein R10 is haloalkyl.

16. A compound as claimed by any one of Claims 1 through 15 wherein R10 is CF_3.

17. A compound as claimed by any one of Claims 1 through 14, wherein R10 is haloalkyloxy.

18. A compound as claimed by any one of Claims 1 through 17 wherein R10 and R11 are each

independently selected from the group consisting of hydrogen, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkyloxy.

19. A compound as claimed by any one of Claims 1 through 14 wherein R10 is selected from the group consisting of C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and aryloxy.

20. A compound as claimed by any one of Claims 1 through 19 wherein R8 and R9 are each independently selected from the group consisting of hydrogen and C_1-C_3 alkyl.

21. A compound as claimed by any one of Claims 1 through 20 wherein R3, and R4 are each independently selected from the group consisting of C_1-C_2 alkyl.

22. A compound as claimed by any one of Claims 1 through 20 wherein R3, and R4 are each independently selected from the group consisting of hydrogen and C_1-C_2 alkyl.

23. A compound as claimed by any one of Claims 6 through 22, wherein X-U is optionally substituted $-S(CH_2)_2$.

24. A compound as claimed by any one of Claims 1 through 23 wherein U is C_1-C_3 alkyl.

25. A compound as claimed by Claim 24 wherein U is saturated.

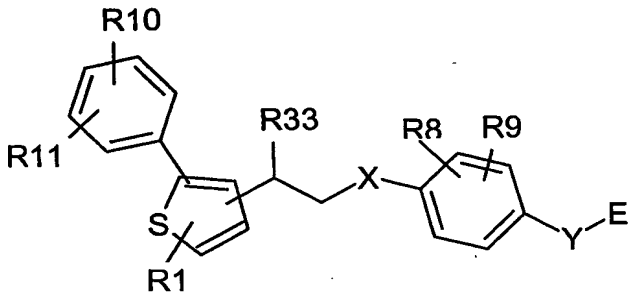
26. A compound as claimed by any one of Claims 1, 2, 3, 4, 23, 24, or 25 wherein U is substituted with C_1-C_3 alkyl.

27. A compound as claimed by any one of Claims 1, 2, 3, 4, 23, 24, or 25 wherein U is substituted with arylC_1-C_4alkyl.

28. A compound as claimed by any one of Claims 23, 24, 25, 26, or 27 wherein one carbon of the U group is replaced with an -O-.

29. A compound as claimed by any one of Claims 1 through 28 wherein R1 is selected from the group consisting of phenyl and pyridyl.

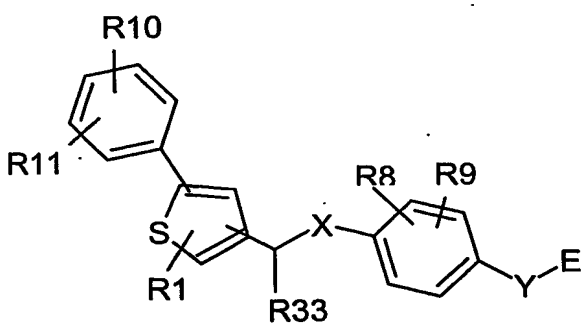
30. A compound as claimed by any one of Claims 1 through 22, or 29 represented by the following Structural Formula II:



wherein R33 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, and arylC_0-C_4 alkyl.

31. A compound as claimed by Claim 30 wherein R33 is arylC_1-C_4 alkyl.

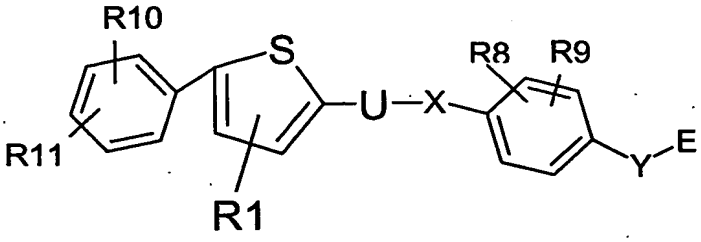
32. A compound as claimed by any one of Claims 1 through 22, or 29 represented by the following Structural Formula III:



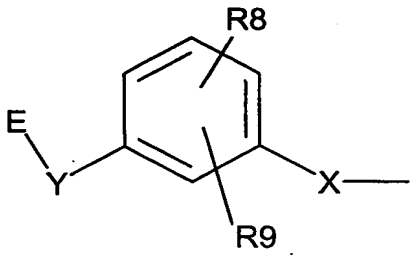
R33 is selected

from the group consisting of hydrogen, C_1-C_3 alkyl, and arylC_0-C_4 alkyl.

33. A compound as claimed by any one of Claims 1 through 29 represented by the following Structural Formula IV:



34. A compound as claimed by any one of Claims 1 through 29 wherein the headpiece of Formula I is:



35. A compound as claimed by any one of Claims 1 through 34 wherein R4 is selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26.

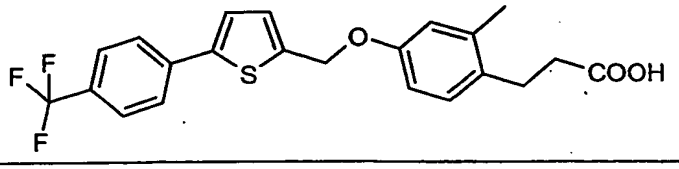
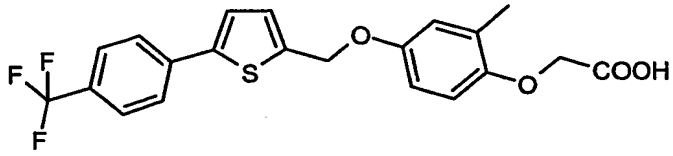
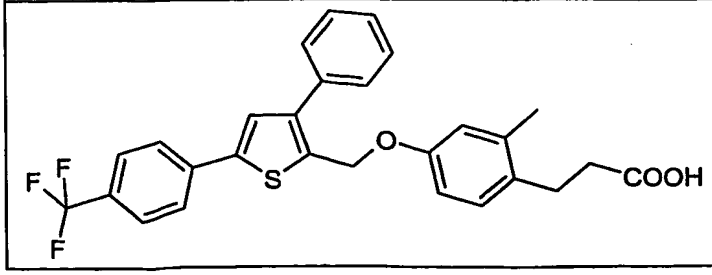
36. A compound as claimed by any one of Claims 1 through 35 wherein E is C(R3)(R4)A.

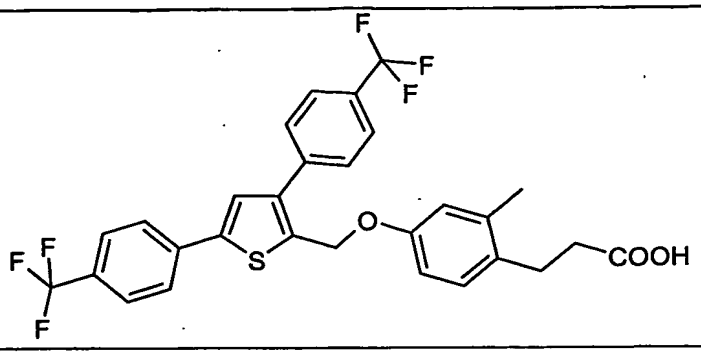
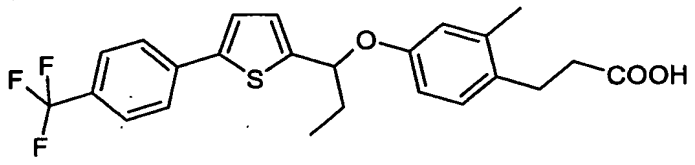
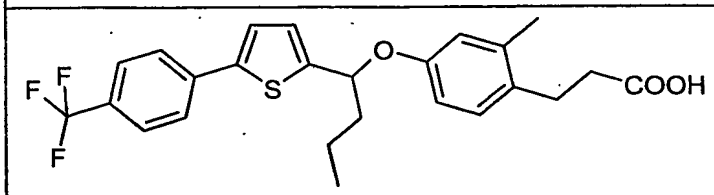
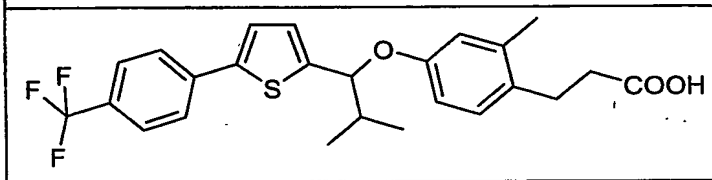
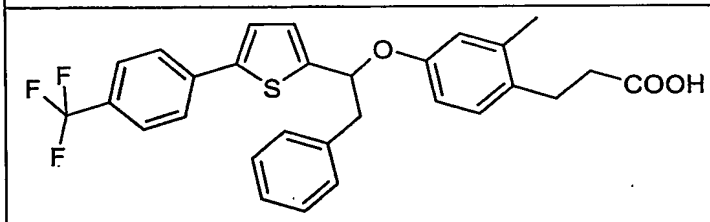
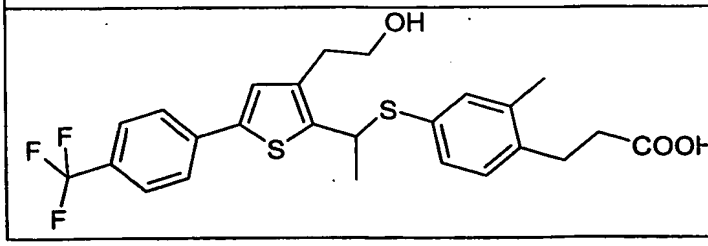
37. A compound as claimed by any one of Claims 1 through 35 wherein A is COOH.

38. A compound as claimed by any one of Claims 1 through 4, wherein the compound is selected from the group consisting of (2-Methyl-4-{2-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propylsulfanyl}-phenoxy)-acetic acid, (2-Methyl-4-{2-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propylsulfanyl}-phenoxy)-acetic acid, 3-(2-Methyl-4-{2-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propylsulfanyl}-phenyl)-propionic acid, and (3-{2-[3-Methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propoxy}-phenyl)-acetic.

39. A compound as claimed by any one of Claims 1 through 4 that is (3-{2-[3-Methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propoxy}-phenyl)-acetic.

40. A compound as claimed by any one of Claims 1 through 4 wherein the compound is selected from the group consisting of

Compound	Name
	3-{2-Methyl-4-[5-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-phenyl}-propionic acid
	{2-Methyl-4-[5-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-phenoxy}-acetic acid
	3-{2-Methyl-4-[3-phenyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-phenyl}-propionic acid

	3-{4-[3,5-Bis-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-2-methyl-phenyl}-propionic acid
	3-(2-Methyl-4-{1-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propoxy}-phenyl)-propionic acid
	3-(2-Methyl-4-{1-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-butoxy}-phenyl)-propionic acid
	3-(2-Methyl-4-{2-methyl-1-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propoxy}-phenyl)-propionic acid
	3-(2-Methyl-4-{1-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-phenyl-ethoxy}-phenyl)-propionic acid
	3-(4-{1-[3-(2-Hydroxy-ethyl)-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid

41. A compound as claimed by any one of Claims 1 through 4 which is selected from the group consisting of {2-Methyl-4-[5-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-phenoxy}-acetic acid and 3-{2-Methyl-4-[5-(4-

trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-phenyl}-propionic acid.

42. A compound as claimed by any one of Claims 1 through 38 which is the S conformation.

43. A compound as claimed by any one of Claims 1 through 38 which is the R conformation.

44. A pharmaceutical composition, comprising as an active ingredient, at least one compound as claimed by any one of Claims 1 through 43 together with a pharmaceutically acceptable carrier or diluent.

45. A method of modulating a peroxisome proliferator activated receptor, comprising the step of activating the receptor with at least one compound as claimed by any one of Claims 1 through 43.

46. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound of Claims 1 through 43.

47. A method of treating Metabolic syndrome in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 43.

48. A method of selectively modulating a PPAR delta receptor comprising administering a compound as claimed by any one of Claims 1 through 43 to a mammal in need thereof.

49. The manufacture of a medicament for use in the treatment and/or prevention of a condition

mediated by nuclear receptors, in particular by a peroxisome proliferator activated receptor, wherein the compound is a compound as claimed by any one of Claims 1 through 43.

50. A method of treating atherosclerosis in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 43.

51. A method for treating or preventing the progression of cardiovascular disease in a mammal in need thereof comprising administering a therapeutically effective amount of a compound as Claimed by any one of Claims 1 through 43.

52. A method as claimed by Claim 51 wherein the mammal is diagnosed as being in need of such treatment.

53. A method of treating arthritis in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound as claimed by any one of Claims 1 through 43.

54. A method of treating demyelating disease in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound as claimed by any one of Claims 1 through 43.

55. A method of treating inflammatory disease in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least

one compound as claimed by any one of Claims 1 through 43.

56. A method as claimed by any one of Claims 53, 54, and 55 wherein such mammal is diagnosed as being in need of such treatment.

57. A compound as Claimed by any one of Claims 1 through 43 for use as a pharmaceutical.

58. A compound as claimed by any one of Claims 1 through 43 wherein the compound is radiolabeled.

59. A compound as disclosed by any one of the Examples herein.

60. All methods disclosed herein of preparing the compounds represented by Structural Formula I.